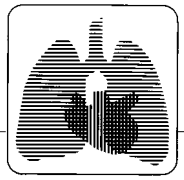

clinical investigations

Prognosis of Patients with Lung Cancer Found in a Single Chest Radiograph Screening*

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Background: **The prognosis of patients with lung cancer is better when the diagnosis is made early; the disease is localized, and radical surgery is possible. Screening for lung cancer with mass radiography or sputum cytology should contribute to a more favorable prognosis. Large-scale screening studies have improved the survival rates for lung cancer but have yielded no reduction in mortality rates.**

Methods: **The histologic types, stages, treatments, and survival rates were studied in 93 men who were found to have lung cancer in a single chest radiograph screening of more than 33,000 men who smoked and were 50 to 69 years old ("screened cases"), and in 239 men of the same age range whose lung cancer was detected through ordinary health care system ("other cases") during the screening period.**

Results: **The distribution of the histology was similar in the two groups, but screening detected more instances of early-stage disease that were resectable more often than in the other group (37 vs 19%). The 5-year survival rate for men in the screened cases was 19%, and that of men in the other cases was 10% (relative risk, 0.65; 95% confidence interval [CI], 0.50 to 0.84). The survival rate of men in the screened cases remained significantly higher than that of men in the other cases even after adjustments for age, smoking status, histology, stage of the disease, and resectability of the disease (relative risk, 0.74; 95% CI, 0.55 to 1.00).**

Conclusions: **According to this study, chest radiograph screening might improve the prognosis of lung cancer. Our results are, however, subject to many factors that were only partially controlled for, and they should be interpreted cautiously.** ***(CHEST 1998; 114:1514–1518)***

Key words: lung cancer; screening; survival

Abbreviation: ATBC Study = Alpha-Tocopherol, Beta Carotene Cancer Prevention Study

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Lung cancer is occurring in epidemic proportions worldwide, and in the United States it accounts for more deaths than breast cancer, pancreatic cancer, and colorectal cancer combined.[1] One of eight

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individuals diagnosed with lung cancer will survive 5 years.[1] Intensive research and the application of combined modality therapy in advanced lung cancer have not changed the prognosis during recent decades. The prognosis is better, however, if the diagnosis is made early when the disease is still localized and is curable with radical surgery.

Frequent screening for lung cancer with mass radiography or sputum cytology could be expected to improve the prognosis. Large-scale screening studies in Britain,[2] Germany,[3] the United States,[4] and Czechoslovakia[5] have demonstrated an increased incidence of lung cancer, an increased resection rate, and an improved survival rate in the screened population. Nevertheless, the studies have shown no significant reduction in mortality. This has, however, been speculated to be due to the failure of randomization.[6] Thus, the role of chest radiograph screening for the early detection of lung cancer is still debatable.

We compared the survival rate of patients whose lung cancer was found in a single chest radiograph screening with the survival rate of men whose lung cancer was detected through ordinary health care system. We also tried to identify variables that could explain the differences in survival rates between the screened and nonscreened groups.

Materials and Methods

The study consisted of two groups of lung cancer patients. The term "screened cases" refers to the group of men whose lung cancer was found during the enrollment of participants in the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (ATBC Study) between 1985 and 1988.[7] The participants were recruited from the total population of men, aged 50 to 69 years, who were living in southwestern Finland (n = 290,406). Men who in the postal survey reported smoking at least five cigarettes/d and who were willing to participate in the trial were scheduled for a systematic chest radiograph examination to exclude lung cancer (n = 33,743). Of these, 93 men were found in the screening chest radiograph to have previously undiagnosed lung cancer; it is this group of men who are called the "screened cases."

The term "other cases" refers to the group of men, 50 to 69 years old, who were diagnosed with lung cancer in one of the screening centers at Turku University Hospital between 1985 and 1988, and to whom invitations to participate in the ATBC Study were sent, but who were not current smokers or who did not respond to the invitation to participate in the ATBC Study (the male population of relevant age in the Turku University Hospital district was about 36,000). These other men (n = 239) were identified through the local hospital discharge register. Lung cancer was found in 74 of those men (31%) by chance in chest radiographs taken for the control of diseases other than lung cancer. The remaining men (n = 165) had contacted their doctor because of symptoms related to lung cancer.

The histological classification of lung cancer was based on a primary assessment in the local pathology laboratories. The cases were grouped into squamous cell cancer, small cell cancer, adenocarcinoma, large cell cancer, and other types of cancer.[8] The diagnosis was based on histology in 74% of the cases in both groups, and on cytology only in 8% of the screened cases and in 4% of the other cases. Clinical staging of lung cancer was based on the American Joint Committee on Cancer classification.[9] Survival follow-up was 5 years.

Mean differences of continuous variables were tested for statistical significance with the *t* test and for the frequency distributions of categorical variables with the χ^2 test. Survival was described using the Kaplan-Meier curve, and the equality of survival was evaluated with the log-rank test. The effect of various factors on the prognosis was assessed and was controlled for using the Cox model.

Results

The prevalence of lung cancer was 2.8/1,000 men in the screened group, and it increased with age from 0.9 among men aged 50 to 54 years to 6.0 in the age group of men aged 65 to 69 years.

The men in the screened cases were slightly younger than those in the other cases. The mean ($\pm$ SD) ages were 61.2 $\pm$ 4.9 years and 62.6 $\pm$ 5.0 years ($p = 0.02$), respectively. Smoking habits also differed between the groups: 91% of the men in the screened cases were current smokers, compared with 58% of the men in the other cases. Six percent of the men in the screened cases had recently stopped smoking, and the smoking status of 2% of the men in the screened cases remained unknown. Thirty-eight percent of men in the other cases had quit smoking, with a quarter of them having quit more than 10 years earlier. The smoking status of 4% of men in the other cases was unknown. Men in both groups who smoked at the time of diagnosis had similar smoking habits: they had smoked 20 cigarettes/d for about 40 years.

The histology of the men in the screened cases was not significantly different from that of the men in the other cases (Table 1). According to clinical staging, lung cancer in men from the screened cases was more limited than in men from the other cases ($p = 0.005$). The treatment of lung cancer was also different in the two groups. Radical surgery was performed on 37% of men with lung cancer from the screened cases and on 19% of men with lung cancer from the other cases ($p < 0.001$). The most important reasons for inoperability in men with limited disease were poor lung function and the presence of other severe diseases. In both groups, 48% of men were treated with radiotherapy or chemotherapy, while 15% of men in the screened cases and 33% of men in the other cases had symptomatic treatment only.

The survival of men in the screened cases was better than among men in the other cases (log-rank, $p < 0.001$; Fig 1). Nineteen percent of men in the screened cases and 10% of men in the other cases were alive 5 years after diagnosis (crude relative risk, 0.65; 95% CI, 0.50 to 0.84). While the main cause of death in both groups was lung cancer, 11% of deaths among men in the screened cases and 8% among men in the other cases were unrelated to lung cancer.

Prognosis according to the histology of lung cancer was different in the two groups: The 5-year prognosis

Table 1—*Characteristics and 5-Year Survival of Patients With Lung Cancer Found in Chest Radiograph Screening and of Patients Diagnosed in the Ordinary Health Care System*

Characteristic	Screened Cases		Other Cases	
	All, n (%)	Survived, n (%)	All, n (%)	Survived, n (%)
Histologic type				
Squamous cell	42 (45)	9 (21)	109 (46)	18 (17)
Adenocarcinoma	23 (25)	6 (26)	47 (20)	4 (9)
Small cell	12 (13)	1 (8)	51 (21)	2 (4)
Large cell	5 (5)	0 (0)	14 (6)	1 (7)
Others or unknown	11 (12)	2 (18)	18 (8)	0 (0)
Total	93 (100)	18 (19)	239 (100)	25 (10)
Stage				
I	50 (54)	14 (28)	72 (30)	17 (24)
II	6 (7)	1 (17)	24 (10)	6 (25)
IIIa	9 (10)	1 (11)	42 (18)	1 (2)
IIIb	12 (13)	2 (17)	39 (16)	0 (0)
IV	15 (16)	0 (0)	60 (25)	1 (2)
Not known	1 (1)	0 (0)	2 (1)	0 (0)
Total	93 (100)	18 (19)	239 (100)	25 (10)
Treatment				
Curative resection	34 (37)	13 (38)	45 (19)	18 (40)
Other	59 (63)	5 (8)	194 (81)	7 (4)
Total	93 (100)	18 (19)	239 (100)	25 (10)

was best for adenocarcinoma (26%) in the screened group, while in the other group prognosis was best for squamous cell carcinomas (17%). Only a few patients were alive 5 years after diagnosis in the other histologic types (Table 1). As expected, the prognosis was best in limited disease (stages I and II), and this did not significantly differ between the groups. In both groups, about 40% of the patients who underwent radical surgery were alive after 5 years.

The screened group had a significantly higher 5-year survival rate than the other group, even after controlling for age, smoking status, histology, stage, and treatment in the Cox model (relative risk, 0.74; 95% CI, 0.55 to 1.00).

Discussion

We studied whether a single chest radiograph screening had a favorable effect on the prognosis of lung cancer. The screened cases consisted of men whose lung cancer was found in the baseline chest radiograph screening during the enrollment of participants to the ATBC Study. The comparison group, "other cases," were men with lung cancer detected through the ordinary health care system. The screened cases were from 10 health care districts, whereas the other cases came from one district (Turku), which provided about 13% of the participants in the ATBC Study. The incidence of lung cancer was similar in the different health care districts; from 1984 to 1988, the age-adjusted incidence of male lung cancer was 59.5/100,000 person-years in Turku and was between 55.7 and 66.9/100,000 person-years in other districts of the ATBC Study. Also, the 5-year survival rate of patients with lung cancer varied little from one region to another (range, 11 to 13%). The access to a primary health care system is easy, prompt, and free of charge all over Finland. A chest radiograph is routine when prolonged respiratory symptoms are presented. Thus, the Turku health care district is thought to represent the whole ATBC Study area.

We found that the 5-year survival rate of lung cancer patients detected in a single chest radiograph screening was better than the rate of other lung cancer patients. Two thirds of men in the other cases were diagnosed because of symptoms, and one third were diagnosed by chance in routine chest radiograph examinations. If the latter group is excluded and if only lung cancer deaths are considered, the difference in survival rates between the two groups is even more pronounced.

If the difference in survival rates between the screened cases and the other cases is real, it reflects the effectiveness of systematic chest radiograph screening in detecting cancer earlier when the disease is still resectable, or it might reflect biases from four well-defined sources; namely, selection, lead time, overdiagnosis, and length-biased sampling.[10]

Selection bias is apparent in our study because the screened men were willing to participate in the

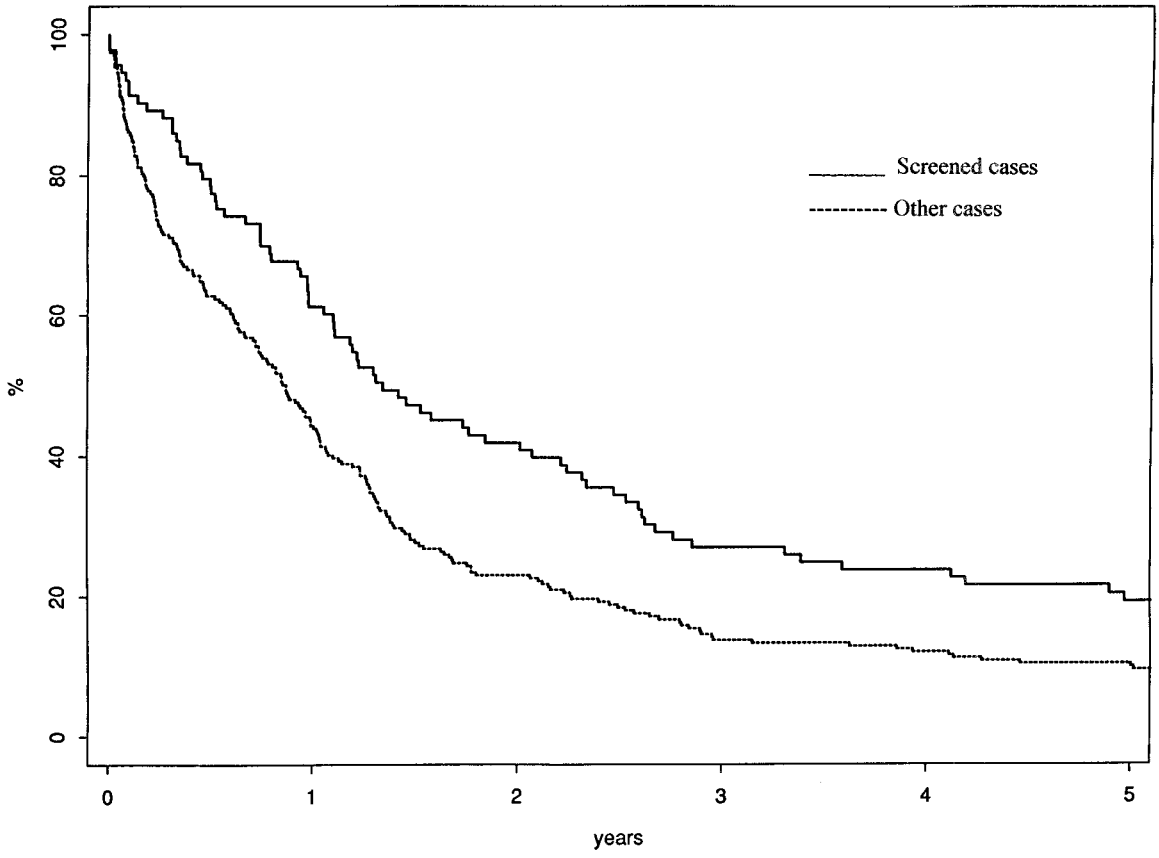

FIGURE 1. Survival of patients with lung cancer that was found during a chest radiograph screening, and survival of patients who were diagnosed in the ordinary health care system.

ATBC Study with a daily intake of one study capsule and follow-up visits three times a year for at least 5 years. In contrast, the other cases consisted of men who were invited to the ATBC Study, but who either were not current smokers or did not respond. Men who were willing to participate in the ATBC Study might differ from those who were not in many ways that could influence their survival. For example, the oldest eligible age group of men was under-represented in the trial; hence, the subjects with lung cancer who were found by screening were somewhat younger than the other subjects. It has been claimed that persons with poor lifestyle habits are less likely to participate in screening and other studies than more health-conscious volunteers. Less health-conscious persons are also more likely to get lung cancer and tend to have a worse prognosis.[10] Also, socioeconomic factors might have an influence not only on lung cancer incidence and mortality but also on the likelihood of treatment[11] and on survival.[12] Unfortunately, we do not have information about the patients' education and economic status. We, therefore, cannot exclude the possible effect of selection bias on prognoses in our comparison groups.

The better prognosis for men from the screened cases might also simply be due to the survival time being measured from an earlier time point during apparent lung cancer (*ie*, lead-time bias). Therefore, we adjusted for stage and resectability as proxies for the phase of cancer progress, but even then survival rate of men in the screened cases remained higher. In fact, this adjustment may lead to overcontrolling of the main result. If screening has no beneficial effect, the cure rates would be expected to be identical in the two groups, and the survival rates in the two groups would eventually reach the same plateau. While it is difficult to reach definitive conclusions regarding the plateau before all patients have died, 5 years of observation shows no evidence of the survival curves coming together toward the same level. Therefore, we consider the effect of possible lead-time bias to be negligible on the results.

Another possible explanation for the observed discrepancy in outcomes is that screening detects lesions that are not clinically important and would not adversely affect the life span of the patient. Many sources of evidence, however, argue against this.

There is little biologic evidence to support the contentions that lung cancer sometimes behaves in a benign fashion and, in contrast to prostate cancer, that clinically unimportant latent lung cancer is infrequently found during autopsy.[1,13–19]

Slowly growing lung cancers have long latent periods and, therefore, are more apt to be found in chest radiograph screening than rapidly growing tumors that progress more quickly to symptoms and death. Slowly growing lung cancers are over-represented in a population screened only once, as in our study. Over-representation of inherently less malignant cases among those detected by screening influences the survival rate favorably. Consequently, the effect of screening appears to be better than it actually is. This is called length bias. Since we do not have any data on the growth rate of lung cancer, we cannot rule out the effect of possible length bias on our results. Nevertheless, the distribution of histological subtypes was similar in both groups, and adjustment for histology did not materially change the better prognosis of the screened cases compared to the other cases.

In conclusion, subjects with cases of lung cancer found through a single chest radiograph screening had a better prognosis compared with cases found through ordinary health care. The results are, however, subject to factors that were only partly controlled and, so, should be interpreted cautiously.

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